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Message-Id: <5E18A91F57D5002034@cmu.unige.ch>
To: jsl@ROCKVAX.ROCKEFELLER.EDU
Subject: Re: Your abstract; Enciclopedia

Dear Joshua,

I am sending you a review of the Brook's book on the emergence of bacterial genetics. This is a preliminary version. Please disregard English faults. I would welcome very much your criticism.

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This is an important book. With a remarkable richness of information on personal, institutional and technical aspects, the author reconstructs the origins of a new discipline, bacterial genetics, that played a relevant role in the "molecular revolution" and even today furnishes theoretical and technical tool to contemporary biology.

>From a historical point of view, the study of the emergence of a new discipline aims to specify the singularities of the new scientific reality which specifically distinguish it from others, in particular a new model of scientific explanation and the formation of a new scientific community with specific characteristics. To identify the origins of a discipline implies a theoretical and historical definition, because it entails the definition of its theoretical core. This is more difficult for contemporary sciences, when the disciplinary status is still being worked out. The main historiographical problem is to determine what should be considered as the real origin of a discipline: New discovery? Existence of a scientific community with an institutional status and specialized journals and congresses? New paradigmatic theory? A new technical framework? The disparate character of these questions does not allow a simple answer and in this particular case microbial genetics has been often considered not as an autonomous discipline, but rather a wonderful tool for classical geneticists, cellular biochemists and physiologists, medical microbiologists and molecular biologists. This is also the consequence of the relevant role played by microbiology in contemporary biological and medical sciences, as an analytical tool for genetics and pharmacology, and a theoretical basis for parasitology and preventive medicine. As it clearly shown in this book, after the important contributions of Pasteur, Koch, Flugge, Beijerinck, the convergence of microbiology with general biology and the merging of different approaches to bacterial morphology, metabolism and genetics (nutrition research, comparative biochemistry, microbial genetics, chemotherapy, cytology, taxonomy and virology) transformed the bacteria into fully blown biological objects. This transformation therefore marks a concurrent shift across a whole range of different subjects and only an interdisciplinary historical analysis can reveal the reasons for this event.

*Book selected
no more than
Hawth.*

The attention with which the author underlines the relevant aspects is remarkable and the book is written with a clarity that does not conceal the complexity and the hard technical aspects of the experiments. For example, Delbruck and Luria's "fluctuation test" (p.58-63) or Lwoff's experiments on the induction of the prophage (p.174-179) are rarely discussed with such a clarity and insight. The structure of the book is arranged logically, instead than chronologically and each chapter corresponds to a chapter of a present-day textbook on bacterial genetics. This implies some reversion of the historical order. For example, Avery transformation experiments, realised in 1941, are discussed in chapter 9, after a chapter devoted to transduction (chap.8) discovered by Zinder and Lederberg in 1952. Furthermore, the authors describes Jacob and Wollman experiments on zygotic induction before speaking of phage and of Lwoff's experiments on phage induction, that were in large part at the origin of Wollman-Jacob experiments (which, by the way are discussed twice, in chap. 5 and chap. 7).

For its organization and content, this book could be considered as an extended historical introduction to the contemporary microbial genetics. This of course is quite useful, and the book should be read by everyone wishing to understand microbiology, but this constitute also its main limit. The book focuses on the history of facts and experiments, rather than ideas, in "key experiments" rather than in theoretical changes. These key experiments are: 1. Beadle-Tatum nutritional mutants in *Neurospora crassa* (the first real insight into the connection between genotype and phenotype). 2. The Luria/Delbruck fluctuation test; 3. Avery, MacLeod, and McCarthy and the Hershey-Chase (1952) experiments, that showed that "genes are made of DNA"; 4. the discovery of mating in *E.coli* by J. Lederberg and Tatum (1946); 5. The demonstration that bacteriophage is capable of undergoing genetic recombination (Delbruck, Bailey, 1946); 6. Lwoff and Gutmann (1950) demonstration that the phage production is a cellular event rather than a population event. Every list of this type is by definition incomplete. My own favourite for adding to the list are the "coitus interruptus experiment" realized by Wollman and Jacob and the Pajamo (Pardee-Jacob-Monod) experiments, that are at the origin of the operon model. One experiment is however considered by the author as central: "It was only when Lederberg and his emulators were able to carry out genetic analysis with *Escherichia coli* K-12 that gene structure in bacterial could be studied. Thus, Lederberg's work became the cornerstone of bacterial genetics." The author describes the experiments and their results, but quite little is said about the theoretical reasons of the choice of a particular experiment to answer a theoretical question or the reasons of the introduction of a new technique. It is not clear, for instance, why "in 1945, Lederberg decided to try to develop a genetic system in a bacterium ... [and] conceived the use of nutritional mutants as a mean of searching for mating in bacterial" (p. 81). The priority assigned to "facts", explains the oddle statement that "it is striking that although transformation is a prominent genetic phenomenon in certain bacteria, the development of bacterial genetics did not depend in any way on the existence of transformation or on the knowledge that the transforming principle was DNA" (p.256), even if, in a footnote, this is considered "an overstatement, since Lederberg was stimulated to begin work on bacterial genetics because of the announcement of the chemistry of the transforming principle".

A few important concepts are ill defined, and as a consequence their historical treatment is misleading. For example, Lederberg in 1950, studying the enzyme *galactosidase*, "concluded that "permeability" factors influenced the apparent activity of the enzyme. It is interesting that Monod's laboratory "rediscovered"

I also disputed Bech.

the role of permeability in the activity of the organism some years later ... Although Monod has received much of the credit for the development of an attractive model of permeability phenomena in bacterial, he was by no means the first". (p. 282, 287). The problem is that permeability as such was well known in the Monod's laboratory already in the late '40s but the idea was refused because "every time a microbiologist has no clear explanation for a nutritional puzzle, he calls upon permeability to conceal his ignorance" (quoted by G. Cohen). Permeability was not "rediscovered", but integrated in a new theoretical model. Another example. Bro~~ok~~* considers the Monod's 1947 model of enzymatic induction a "selective" one: "It is interesting to note that in this model the substrate does not play an "instructive" role but merely a "selective" or regulatory role, and hence the model is reminiscent of the operon model ultimately developed" (p.273). At the contrary, this model was instructive, like in Pauling's immunochemical model, because "there is proof that the substance plays an important and decisive part in the synthesis, although specific genes are implicated in determining the competence to adapt" (Monod, 1950). Monod himself insisted on the discontinuity with the operon model. By the way, the author himself considers that even in the late '50s "Monod was still thinking of an "instructive" role for the inducer, and it was only after Leo Szilard suggested a negative repressor model that Monod became enthusiastic for it" (p. 293).

The attitude to find out precursors and anticipations is spread in the book and that often hides the relevant theoretical breakthroughs. Brook considers that the Emerson template model (1945), not very dissimilar from other stereospecific models proposed during the '40s, "bears a striking analogy with the Watson/Crick model for DNA, with the gene and its template being equivalent to the two complementary strand of the DNA polynucleotide." This statement hides an important theoretical innovation, that is that from a genetic point of view the important thing in the double helix model is not the complementary structure but the fact that this structure allows a linear message to be carried on and "it follows that in a long molecule many different permutations are possible, and it therefore seems likely that precise sequence of the bases is the code which carries genetic information ... the specificity of a piece of nucleic acid is expressed solely by the sequence of its bases, and [...] this sequence is a (simple) code for the amino acid sequence of a particular protein" (Watson-Crick, 1953). The concept of information and programme are almost totally absent from this book, and in my view that is its main limit. The author considers that the origin of molecular biology lies on the merging of genetic with biochemistry, as in the classical tradition of physiological genetics, a la Troland or Goldschmidt: "It was through an intimate merging of bacterial genetics with biochemistry and physiology that the central processes of cellular metabolism were to be understood. Through this amalgamation, the fundamental dogma of modern biology: DNA -> RNA -> protein, was to emerge". This is quite misleading, because the central dogma, as proposed by Francis Crick in 1958, derived exclusively from considerations on the transfer of genetic information, and in this paper Crick accurately avoided any reference to biochemical aspects. Only in the '60s, after the elaboration of the operon model and the origin of the concept of messenger, the physiological aspects of the central dogma were worked out.

Concentrating on the history of the contemporary aspect of a discipline can easily mask the historical relevance of failed research programmes that have not been incorporated into the new disciplines, but which nevertheless played a relevant historical role. To give an example, before the origins of molecular biology,

during the 1940s, the plasmagene theory - which did not coincide, as the author seems to imply, with the problem of cytoplasmic inheritance, spread widely within the biological and medical sciences, as an attempt to provide a unified explanation of the self replicating phenomena in microbiology, genetics, biochemistry and medicine. This theory dominated a large part of biological thinking in that period, and certainly had a remarkable impact on the development of many biological disciplines, though it is today little known, even to the historian of science. This was particularly true for embryologists, in search of a causative explanation of the nucleo-cytoplasmic relationships during differentiation, and Sonneborn himself in 1949 was obliged to warn them about the role of such purely hypothetical plasmagenes in cell differentiation. However, the idea of 'self-reproducing units' was widely diffused even between virologists and geneticists. As put by Pontecorvo in 1949, "the genetical approach, that is, the study of sub-cellular 'self-reproducing' units, is now as essential to the understanding of heredity, variation and evolution as it is in bridging the gap between biochemistry and biology. At the level of these units, biological structure and biochemical activity tend to become one". Delbruck model of "alternating dynamic states" was inside this model, that however was abandoned and replaced by the new explanation based on information and programme, in which biological specificity and chemical aspects are sharply separated.

Brook himself is a bacterial geneticist and his views on the origin of his own disciplines, from "the inside", is also a direct testimony of this historical process. This should be kept in mind, as many of the judgements on people, experiments and institutions reflect the personal experience of the author, even his likes and dislikes. One of the scientists the author dislikes is Monod, who according to different passages was always anticipated, by Karstrom and Yudkin for enzymatic induction, by Vogel and Szilard for the repression model, by Jacob, who "had the key insight on the operon model". In particular Monod was clearly anticipated by Lederberg who in 1951 "presented the key ideas that later became the Monod canon ... the essential leads for the subsequent work of Monod and his collaborators. Why were ignored by Monod? Although some chauvinism may have been involved, my contention is that the evidence was genetic rather than physiological, which was what Monod was seeking." This explanation is clearly doubtful, because Monod was seeking for both genetic and physiological explanation, and he was one of the few actors of this story to have a classical genetic background, having spent a year at Caltech in Morgan laboratory in 1936 and having translated in French a book by Sturtevant on *Drosophila* genetics. There is no space for an accurate analysis of this problem, but reading only this book one can wonder why Monod is considered by Lwoff as "the architect of molecular biology", because "between 1948 and 1963 the main problems of the induced synthesis of enzymes were solved and molecular biology was created ex nihilo". The history of microbial genetics is here clearly interpreted through the lenses of Max Delbruck and Joshua Lederberg. This of course is very useful, as these two scientists could be considered as the founders of the new paradigm, but it cannot be considered exhaustive. Even the archive sources and personal reminiscences is mainly limited to the American and English sources. Probably, a look at the Monod Papers, collected since 1987 in the Archives of the Institute Pasteur, should have mitigated some hasty judgements on Monod's role in molecular biology.

Notwithstanding some minor historical feebleness and some one-sidedness, or perhaps even because of them, because they are revealing, coming from the inside of the discipline, this book makes a fascinating reading and it should be considered an indispensable tool for anyone interested in the history of

contemporary biological sciences.